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Baxter

March 26, 2002

Dear Healthcare Provider,

Subject: Thrombotic Events and Immune Globulin Intravenous (IGIV)

There are many articles in the literature that describe the occurrence of thrombotic events in patients receiving immune globulin intravenous (1-28*). In view of the serious nature of these reported thrombotic events, we wish to draw your attention to the package insert for Gammagard S/D, which includes a statement to this effect under the 'Precautions' section of the document. The precautionary statement is as follows:

There is clinical evidence of a possible association between Immune Globulin Intravenous (Human) (IGIV) administration and thrombotic events. The exact cause of this is unknown; therefore, caution should be exercised in the prescribing and infusion of IGIV in patients with a history of cardiovascular disease or thrombotic episodes.

From both the medical literature and our internal pharmacovigilance/quality assurance program, we continue to receive reports describing serious thrombotic (vascular occlusive) events possibly associated with the infusion of immune globulin intravenous (IGIV). Analysis of these events indicates that the etiology is complex and multi-variant and the cause of this association is not clearly understood.

However, our own recent analysis of serious adverse events reported via pharmacovigilance, has identified rapid infusion of immune globulin intravenous as a possible risk factor. For example,

Grillo and co-workers report on the use of rapid infusion of immune globulin intravenous in patients with neuromuscular disorders in the November 2001 issue of the journal Neurology, Vol. 57 (pages 1699 – 1701). Their abstract and discussion claim safety and convenience of this practice in their population of patients and the final sentence of their abstract states "Rapid infusion IVIg can be given safely and conveniently in many patients with neuromuscular disorders." While this is accurate for the majority of their patients, the authors report 89 adverse events in 341 rapid infusions in 50 patients, 3.5% of which were considered "major." This amounted to a "major" event in 11 out of 50 patients (22%).

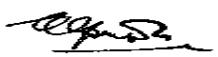
It is these "major" events, and their frequency, which is of concern to us as these events included chest pain, myocardial infarction, congestive cardiac failure, severe headache requiring hospitalization, pulmonary embolism and "transfusion related acute lung injury." These are serious events almost certainly directly related to the rapid infusion protocol (reaching as high as 800 ml/hour) in what is essentially an at-risk population.

It is strongly recommended that clinicians and other health care workers such as pharmacists and nurses who may be associated with the therapeutic administration of immune globulin intravenous, read and follow the package insert.

In the event where there is a possible risk of a thrombotic event, we strongly recommend that the infusion concentration should be no more than 5%, and the infusion rate should be initiated no faster than 0.5 milliliter per kilogram body weight per hour and **advanced slowly** only if well tolerated to a maximum rate of 4 milliliter per kilogram body weight per hour. In other words, the rate of infusion and percent of the solution concentration should be flexible and targeted to the safety of the patient rather than convenience.

Please refer to the enclosed package insert for more complete prescribing information. If you have any further questions or concerns regarding this letter, please call Baxter BioScience Medical Affairs Department at (800) 423-2862.

Sincerely,



Edward Gomperts, MD
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